The prevalence and physiological impacts of centrilobular and paraseptal emphysema on CT in smokers with Preserved Ratio Impaired Spirometry


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The prevalence and physiological impacts of centrilobular and paraseptal emphysema on CT in smokers with Preserved Ratio Impaired Spirometry

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Conflicts of interest
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None of these companies had a role in the design or analysis of the study or in the writing of the
manuscript. Other authors have no conflict of interest to declare.

List of all abbreviations
COPD = chronic obstructive pulmonary disease, PRISm = preserved ratio impaired spirometry,
PSE = paraseptal emphysema, CLE = centrilobular emphysema, ADE = advanced destructive
emphysema, FVC = forced vital capacity, FEV₁ = forced expiratory volume in 1 second, TLC =
total lung capacity, FVC/TLC<sub>CT</sub> = ratio of forced vital capacity to total lung capacity measured on
CT

Take-home message
Centrilobular and paraseptal emphysema were observed in approximately 43-46% of smokers with preserved ratio impaired spirometry. Centrilobular emphysema, but not paraseptal emphysema, was closely associated with air-trapping in these smokers.
Centrilobular emphysema (CLE) and paraseptal emphysema (PSE) are observed in smokers with Preserved Ratio Impaired Spirometry (PRISm, defined as the ratio of forced expiratory volume in 1 second (FEV₁) to forced vital capacity (FVC) ≥0.7 and FEV₁<80%), but their prevalence and physiological impacts remain unestablished. This multicenter study aimed to investigate its prevalence and to test whether emphysema subtypes are differently associated with physiological impairments in smokers with PRISm.

Both never and ever smokers aged at ≥ 40 years who underwent CT for lung cancer screening and spirometry were retrospectively and consecutively enrolled at three hospitals and a clinic. Emphysema subtypes were visually classified according to the Fleischner system. Air-trapping was assessed as the ratio of FVC to total lung capacity on CT (FVC/TLC_{CT}).

Of 1046 never-smokers and 772 smokers with >10 pack-years, the prevalence of PRISm was 8.2 % and 11.3%, respectively. The prevalence of PSE and CLE in smokers with PRISm was comparable to that in smokers with normal spirometry (PSE 43.7% vs 36.2%, p=1.00, CLE 46.0% vs 31.8%, p=0.21), but higher than that in never-smokers with PRISm (PSE, vs 1.2%, p<0.01, CLE, vs 4.7%, p<0.01) and lower than that in smokers with airflow limitation (PSE, vs 71.0%, p<0.01, CLE, vs 79.3%, p<0.01). The presence of CLE but not PSE was independently associated with reduced FVC/TLC_{CT} in smokers with PRISm.

Both PSE and CLE were common, but only CLE was associated with air-trapping in smokers with PRISm, suggesting different physiological roles of these emphysema subtypes.

**Keywords**

Computed tomography, Lung imaging, Spirometry, Emphysema, Pulmonary function
Main body (2711/3000 words)

Introduction

Preserved Ratio Impaired Spirometry (PRISm), defined as reduced forced expiratory volume in 1 second (FEV₁) without airflow limitation on spirometry, is increasingly recognized as a major non-obstructive spirometry disorder [1]. The prevalence of PRISm is 7.1%–12.5% in adults [2–4] and the presence of PRISm is associated with higher risk of mortality in never and ever smokers [2,4]. In smokers, PRISm is also considered the transitional state to chronic obstructive pulmonary disease (COPD) that is characterized by airflow limitation on spirometry and persistent respiratory symptoms [2,5]. However, the management of smokers with PRISm is still challenging due to the clinically heterogenous manifestations. Indeed, a subgroup of smokers with PRISm could develop COPD and show greater mortality than smokers with normal spirometry, but other smokers with PRISm could remain clinically stable over time and even return to normal on follow-up spirometry [3,6]. Therefore, further understanding of clinical features is warranted to improve the outcomes of PRISm.

Computed tomography (CT) is widely used to screen for lung cancer in real-world practice, providing structural information on the airway and parenchyma simultaneously. A previous study showed that radiological abnormalities of the lungs and chest wall such as paraseptal emphysema (PSE), airway wall thickening, diaphragm eventration, and transverse internal thoracic diameter are more frequent in smokers with PRISm than those with normal spirometry [7]. Subsequently, the Fleischner Society published a visual classification system for emphysema [8] to describe the localization of centrilobular emphysema (CLE), PSE and panlobular emphysema on CT. The use of this system has allowed showing that CLE and PSE are common in smokers with and without airflow limitation [9,10]. Moreover, CLE is associated with airflow limitation, lung hyperinflation, and exacerbation frequency, and even mild signs of CLE predict poor prognosis,
whereas PSE is less associated with physiological impairments than CLE [10–12]. These results suggest that the differential emphysema subtypes may contribute to the heterogeneous presentations of smokers with PRISm.

Air-trapping predicts adverse respiratory outcome and progression to COPD in smokers without airflow limitation [13,14] and the ratio of forced vital capacity to total lung capacity on CT (FVC/TLC\textsubscript{CT}) as a conceptual surrogate for air-trapping predicts future worsening of symptoms, exacerbation, and progression to COPD in smokers with PRISm [15]. However, little is known about the morphological basis on air-trapping in these smokers. Therefore, this study tested the hypothesis that CLE and PSE would differentially affect physiological function in smokers with PRISm. Specifically, the study aimed 1) to explore whether the prevalence of CLE and PSE in smokers with PRISm differs from that in never-smokers with PRISm and smokers with normal spirometry and airflow limitation; and 2) to test whether CLE and PSE are associated with physiological impairments, particularly air-trapping, in smokers with PRISm.

Material and Methods

Study design (subjects)

This was a multicenter, retrospective study conducted in three hospitals (Tsukuba Medical Center, Kitano Hospital, and Takeda Hospital) and a general clinic (Terada Clinic). In Japan, hospitals and clinics provide medical checkup program in which chest CT scan for lung cancer screening are offered to all adults regardless of smoking status. In this study, we consecutively enrolled never and ever smokers aged 40 years or older who underwent inspiratory CT for lung cancer screening and spirometry. Subjects with a history of lung resection, chest CT abnormalities extending to more than one lobe (such as consolidations, atelectasis, tumors, pneumothorax and thoracic deformity), missing information on smoking status or light-smokers (< 10 pack-years),
more than 90 days between spirometry and CT scanning or insufficient inspiratory chest CT (defined as FVC > TLC\textsubscript{CT} [15]) were excluded (Figure 1). The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committees (approval R1660-3 and R2751). Written consent was waived because of the retrospective nature of the study.

CT acquisitions, spirometry, and total lung capacity measured on CT

All chest CT scans were acquired at full inspiration. Images at 0.5 to 1.25mm slice thickness were reconstructed using sharp kernels. Spirometry was conducted without bronchodilator and evaluated in each facility by well-trained technicians according to the statement of the American Thoracic Society/European Respiratory Society [16]. Predicted FEV\textsubscript{1} and FVC values were calculated using the LMS method reference equations taking age, gender, and height into account [17]. Subjects were classified as having PRISm (FEV\textsubscript{1}/FVC ≥ 0.7 and FEV\textsubscript{1} %pred <80%), airflow limitation (FEV\textsubscript{1}/FVC <0.7) or normal spirometry (controls; FEV\textsubscript{1}/FVC ≥0.7 and FEV\textsubscript{1} %pred ≥80%). The total lung capacity (TLC\textsubscript{CT}) was calculated on full inspiratory CT using a SYNAPSE VINCENT volume analyzer (FUJIFILM Medical, Tokyo, Japan), and TLC\textsubscript{CT} % predicted was calculated based on the predicted values [18]. Air-trapping was assessed by the ratio of FVC to TLC\textsubscript{CT} as previously reported [15]. A lower FVC/TLC\textsubscript{CT} indicates more severe air-trapping. Additionally, validation of FVC/TLC\textsubscript{CT} as a measure of air-trapping was performed using full inspiratory and end-tidal expiratory CT available from a part of the study population who also participated in a different ongoing prospective airway disease cohort. By using paired inspiratory and expiratory CT, well-established CT markers for air-trapping, including expiratory low attenuation volume %, expiratory mean lung density, and the ratio of expiratory to inspiratory mean lung density ratio, were calculated [19]. In the study, smokers aged 40 years or older underwent a pair of inspiratory and expiratory chest CT with written informed consent [20].

Visual CT analysis
Six CT-experienced pulmonologists with at least 5-year experiences and a chest radiologist with 15-year experience performed visual emphysema analysis based on the Fleischner Society classification system [8]. The images were viewed at window width 700 Hounsfield Unit and window level -750 Hounsfield Unit according to the Fleischner Society’s recommendation [8]. CLE was classified as trace, mild, moderate, confluent or advanced destructive, while PSE was classified as mild or substantial [8]. The category of panlobular emphysema was not used in this study, as it is applied to patients with α1-antitrypsin deficiency [8]. Before assessing visual emphysema score in the study population, the analysts scored training CT datasets and reviewed substantial discordance to obtain consensus. Each CT scan was assessed by two CT-experienced pulmonologists without knowledge of clinical information and the discordances were adjudicated by a chest radiologist. Further details are provided in Supplemental Materials.

**Statistical Analysis**

The weighted kappa coefficient was calculated for interobserver variability in the visual emphysema assessments. The severity of CLE (none trace/mild/moderate/confluent/advanced destructive) was weighted from 0 to 5, and that of PSE (none/mild/substantial) was weighted from 0 to 2. Data are expressed as the mean ± standard deviation (SD) unless indicated. Subjects’ characteristics were compared using Fisher’s exact test or chi-squared test for categorical data and Student’s t-test for continuous variables. The Bonferroni correction method was used to adjust for multiple comparisons. Additionally, the question of whether the presence of PSE and CLE could affect FVC/TLC_{CT} was explored using multivariable linear regression models that included age, gender, BMI, smoking pack-years (as a dichotomous variables, < or ≥ 20 pack-year), smoking status, facilities, and the presence of PSE/CLE as independent variables. Statistical analyses were performed using R statistical software version 4.0.1 and JMP Pro version 16.1.0. A P value less than 0.05 was considered statistically significant.
Results

Interobserver agreement and reliability of air-trapping index

Interobserver agreement for grades of PSE and CLE ranged from moderate to almost perfect. The weighted kappa coefficients for grades of PSE ranged from 0.73 to 0.94 and those of CLE ranged from 0.83 to 0.99 (Supplemental Table1). In smokers who also participated in a different prospective study with written informed consent and underwent a pair of inspiratory and expiratory CT (n=67), FVC/TLC_CT was well correlated with low attenuation volume % under -856 HU in expiratory CT, which is an established marker of air-trapping (Supplemental Table2 and 3) [19].

Clinical and radiological characteristics of never-smokers and smokers with normal spirometry, PRISm, and airflow limitation

As shown in Figure 1, 1818 subjects (1091 male and 727 female) were divided into 1046 never-smokers and 772 substantial smokers (with ≥10 pack-years). Never-smokers and smokers were further classified into those with normal spirometry, PRISm, and airflow limitation, and their features are compared in Table 1. The prevalence of PRISm and airflow limitation in smokers was higher than that in never smokers (11.3% vs 8.2% for PRISm and 21.9% vs 4.4% for airflow limitation, respectively). The pulmonary functions of PRISm in smokers did not differ from those in never-smoker. For any lung function category, the prevalence of PSE and CLE was higher in smokers than in never smokers. This trend is visualized in Figure 2.

The prevalence of CLE in never smokers with airflow limitation was higher than in never smokers with normal spirometry (10.9% vs 1.9%, p = 0.04), while the prevalence of PSE and CLE in never smokers with PRISm did not differ from that in never smokers with normal spirometry (PSE, 1.2% vs 2.5%. p=1.00, CLE, 4.7% vs 1.9%, p=1.00).
When compared within smokers, the prevalence of PSE and CLE in PRISm was comparable to normal spirometry (PRISm vs normal spirometry, PSE 43.7% vs 36.2%, p =1.00, CLE 46.0% vs 31.8%, p =0.21), but lower than those of airflow limitation (PRISm vs airflow limitation, PSE 43.7% vs 71.0%, p<0.01, CLE 46.0% vs 79.3%, p<0.01). Table 2 and Figure 3a show the detail of CLE and PSE categories in never smokers and smokers with normal spirometry, PRISm, and airflow limitation. Moreover, as shown in Figure 3b, the presence of PSE was significantly associated with the presence of CLE in smokers with PRISm (chi-squared test p <0.01).

**Functional impacts of PSE and CLE in smokers with PRISm**

As shown in Table 3, when smokers with PRISm were divided into those with and without CLE, TLC<sub>CT</sub> was higher and FVC/TLC<sub>CT</sub> was lower in the PRISm smokers with CLE than those without CLE, while FEV<sub>1</sub>, FVC, and FEV<sub>1</sub>/FVC did not differ between the two groups. Moreover, as shown in Table 4, in multivariable models, the presence of CLE but not the presence of PSE was associated with reduced FVC/TLC<sub>CT</sub> in smokers with PRISm independent of age, sex, body size, pack-years, and smoking status. When including CLE, PSE, and their interaction term in the same multivariable model, there was no significant interaction between CLE and PSE on FVC/TLC<sub>CT</sub> (p=0.85). In the model without the interaction term, the presence of CLE was associated with reduced FVC/TLC<sub>CT</sub> independent of the presence of PSE. Figure 4 shows representative CT images of two smokers with PRISm. No visual sign of emphysema was found in case (a) (FEV<sub>1</sub>/FVC = 0.80, % predicted FEV<sub>1</sub> = 73.5%, and FVC/TLC<sub>CT</sub> = 86.7%), whereas both PSE and CLE were found in case (b) (FEV<sub>1</sub>/FVC = 0.75, % predicted FEV<sub>1</sub> = 71.5%, and FVC/TLC<sub>CT</sub>=58.9%).

**Discussion**

This large multicenter study showed that the PRISm was found in 11.3% of smokers and
8.3% of never-smokers and that the prevalence of PSE and CLE in the smokers with PRISm (44.6% and 46.7%) was higher than that in never-smokers with PRISm, comparable to smokers with normal spirometry, and lower than smokers with airflow limitation. Furthermore, the multivariable analysis demonstrated that the presence of CLE was independently associated with a reduction in FVC/TLC_CT in smokers with PRISm. Collectively, these findings suggest that PSE and CLE are common in smokers with PRISm and the presence of CLE, but not PSE, is associated with air-trapping in smokers with PRISm.

Despite increasing recognition of PRISm, appropriate personalized management remains to be established. The difficulty is mainly due to the heterogeneous clinical manifestations of PRISm. Indeed, 25.1-32.6% of PRISm develop COPD, but the rest remain in the PRISm group or even transitioned to the normal spirometry group over time [2,3,6]. A recent longitudinal study showed that increased air-trapping, expressed as a reduced FVC/TLC_CT, is associated with increased disease progression in smokers with PRISm [15]. However, no report has examined the morphological changes underlying air-trapping in PRISm. Therefore, the observed association between CLE and FVC/TLC_CT in smokers with PRISm substantially extends the previous finding and suggests that a visual CT finding of CLE can be a promising marker to identify high-risk individuals among smokers with PRISm. Since no established treatment is available, future studies should investigate whether bronchodilators can improve air-trapping and prevent COPD development in smokers with PRISm and CLE.

In multivariable analyses, CLE but not PSE was associated with FVC/TLC_CT in smokers with PRISm. Pathological examinations of smokers’ lungs and COPD lungs have shown that the small airways are a major pathological site in CLE, causing airflow limitation and air-trapping [21–23], whereas the small airways are relatively preserved in PSE [24]. These pathological findings are consistent with a CT study showing that nonemphysematous gas-trapping regions, presumably
induced by the small airway disease, are less severe in smokers with PSE than in those with moderate to severe CLE [25]. Therefore, CLE but not PSE could develop in association with small airway disease and induce air-trapping in smokers with PRISm.

This study confirmed the applicability of the Fleischner emphysema subtyping system to CT obtained at clinical practices, even outside well-established cohorts. Although quantitative measurements of emphysema have been used especially in research [26], the visual assessment complements quantitative measurements and might be more sensitive in detecting tiny parenchymal changes in smokers without airflow limitation [27].

The prevalence of PSE and CLE in smokers with PRISm did not differ from those with normal spirometry. This is not consistent with a previous report showing that PSE was more prevalent in GOLD-Unclassified (synonymous with PRISm) than smokers with normal spirometry while the prevalence of CLE did not differ [7]. Furthermore, the prevalence of PSE and CLE in normal spirometry and PRISm (PSE 36.2% and 43.7%, CLE 31.8% and 46.0%) in this study was higher than those reported in the previous report (PSE 17% and 33%, CLE 22.5% and 27%). This might be because this study used the Fleischner Society classification system to detect emphysema subtype more accurately and sensitively, including trace CLE which involved <0.5% of the lung zone [8].

CLE and PSE in never smokers were also evaluated. Previous studies have shown that airflow limitation is not associated with emphysema on CT in never smokers [28,29], but very little is known about emphysema subtypes in never smokers. Therefore, understanding of structure-function relationship in never smokers is expanded by the present data showing that the prevalence of CLE, but not PSE, was higher in never smokers with airflow limitation than those with normal spirometry while no difference was found between normal spirometry and PRISm.

This study assessed air-trapping using FVC/TLC\textsubscript{CT}. Although a previous report
established this index as an air-trapping index [15], we also confirmed the validity by showing the close association between FVC/TLC$_{CT}$ and low attenuation volume % on expiratory CT using a subgroup of the present study population. It should be also noted that TLC$_{CT}$ measured in the supine position is usually lower than TLC measured in the seated position by plethysmography, but TLC$_{CT}$ is well correlated with TLC measured by plethysmograph [30,31]. Therefore, FVC/TLC$_{CT}$ might be reliable air-trapping surrogate index in daily practice when lung subvolumes such as residual volume and TLC or a pair of inspiratory and expiratory chest CT are unavailable.

The study strengths include the variety of facilities, the large sample size, the use of a simple established protocol for visual assessment of emphysema subtypes and the use of double-reading system to minimize the interobserver variability. However, there are some limitations. Pulmonary functions in the CT lung screening were analyzed using prebronchodilator spirometry because postbronchodilator spirometry is not routinely performed in lung cancer screening program. The quantitative assessment of emphysema could not be conducted because of a variety of CT scanner machines and reconstruction kernels. There was a sex imbalance between never and ever smokers. The retrospective nature of the study may generate selection bias, for example, in relation to the study period of each facility and missing demographic data.

In conclusion, the prevalence of both PSE and CLE on CT in smokers with PRISm was higher than that in never-smokers with PRISm. In smokers with PRISm, the presence of CLE, but not PSE, was associated with air-trapping, suggesting different physiological roles of PSE and CLE. Visual emphysema subtyping on CT with the Fleischner Society classification system can help clinicians understand the pathophysiology of smokers and take a more personalized approach to smokers with PRISm.

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**Table 1. Characteristics of subjects according to lung function categories and smoking history**

<table>
<thead>
<tr>
<th></th>
<th>Subjects with normal spirometry</th>
<th>Subjects with PRISm</th>
<th>Subjects with airflow limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never-smoker</td>
<td>Smoker</td>
<td>Never-smoker</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>914</td>
<td>516</td>
<td>86</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.7 ± 10.4</td>
<td>57.2 ± 10.7</td>
<td>62.4 ± 10.3</td>
</tr>
<tr>
<td>No. of males*</td>
<td>358 (39.2%)</td>
<td>450 (87.2%)†</td>
<td>33 (38.4%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 3.8</td>
<td>24.0 ± 3.3 †</td>
<td>24.2 ± 4.6</td>
</tr>
<tr>
<td>Smoking status, current*</td>
<td>0 (0%)</td>
<td>366 (70.9%)†</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pack-years, ≥ 20 pack-year*</td>
<td>0 (0%)</td>
<td>307 (59.5%)†</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>FVC (predicted %)</td>
<td>97.6 ± 11.7</td>
<td>96.8 ± 10.8</td>
<td>74.4 ± 8.7</td>
</tr>
<tr>
<td>FEV₁ (predicted %)</td>
<td>99.7 ± 11.6</td>
<td>97.2 ± 10.6 †</td>
<td>73.1 ± 7.3</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.81 ± 0.05</td>
<td>0.79 ± 0.05 †</td>
<td>0.78 ± 0.05</td>
</tr>
<tr>
<td>TLC&lt;sub&gt;CT&lt;/sub&gt; (predicted %)</td>
<td>86.9 ± 12.3</td>
<td>85.1 ± 11.7 †</td>
<td>74.7 ± 12.3</td>
</tr>
<tr>
<td>FVC/TLC&lt;sub&gt;CT&lt;/sub&gt; (%)</td>
<td>70.4 ± 10.6</td>
<td>71.3 ± 9.7</td>
<td>61.4 ± 10.5</td>
</tr>
<tr>
<td>The prevalence of PSE*</td>
<td>23 (2.5%)</td>
<td>187 (36.2%) †</td>
<td>1 (1.2%)</td>
</tr>
<tr>
<td>The prevalence of CLE*</td>
<td>17 (1.9%)</td>
<td>164 (31.8%) †</td>
<td>4 (4.7%)</td>
</tr>
</tbody>
</table>

Except where indicated, numbers are means ± standard deviations.
BMI = body mass index, FVC = forced vital capacity, FEV<sub>1</sub> = forced expiratory volume in 1 second, TLC<sub>CT</sub> = total lung capacity measured on CT, FVC/TLC<sub>CT</sub> = ratio of forced vital capacity to total lung capacity measured on CT, PRISm = preserved ratio impaired spirometry, PSE = paraseptal emphysema, CLE = centrilobular emphysema
* Data are numbers of subjects, with percentages in parentheses.
† The value is statistically significant (p value <0.05) compared to never smoker within the same lung function category.
‡ The value is statistically significant (adjusted p value <0.05, adjusted by Bonferroni method) compared to never smoker within the same lung function category. The adjusted p values compared PRISm and other lung function categories in smokers were as follows: PSE, vs normal spirometry, p=1.00, vs airflow limitation, p<0.01 and CLE, vs normal spirometry, p=0.21, vs airflow limitation, p<0.01.
Table 2. The distribution of emphysema subtypes in never and ever smokers according to lung function categories

<table>
<thead>
<tr>
<th></th>
<th>Subjects with normal spirometry</th>
<th>Subjects with PRISm</th>
<th>Subjects with airflow limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never-smoker</td>
<td>Smoker</td>
<td>p-value</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>914</td>
<td>516</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PSE, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>891 (97.5%)</td>
<td>329 (63.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mild</td>
<td>10 (1.1%)</td>
<td>63 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>Substantial</td>
<td>13 (1.4%)</td>
<td>127 (24.0%)</td>
<td></td>
</tr>
<tr>
<td>CLE, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>None</td>
<td>897 (98.1%)</td>
<td>352 (68.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Trace</td>
<td>16 (1.8%)</td>
<td>90 (17.4%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (0.1%)</td>
<td>49 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0%)</td>
<td>17 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Confluent</td>
<td>0 (0%)</td>
<td>1 (0.2%)</td>
<td></td>
</tr>
<tr>
<td>ADE</td>
<td>0 (0%)</td>
<td>7 (1.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are numbers of patients, with percentages in parentheses.
PRISm = preserved ratio impaired spirometry, PSE = paraseptal emphysema, CLE = centrilobular emphysema, ADE = advanced destructive emphysema
Table 3. Characteristics of smoker with PRISm

<table>
<thead>
<tr>
<th></th>
<th>Absent CLE</th>
<th>Present CLE</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>47</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.9 ± 10.8</td>
<td>63.0 ± 11.0</td>
<td>0.71</td>
</tr>
<tr>
<td>No. of males*</td>
<td>40 (85.1%)</td>
<td>36 (90.0%)</td>
<td>0.72</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 3.8</td>
<td>23.5 ± 3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking status, current*</td>
<td>29 (61.7%)</td>
<td>28 (70.0%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Pack-years, ≥ 20 pack-year*</td>
<td>37 (78.7%)</td>
<td>35 (87.5%)</td>
<td>0.43</td>
</tr>
<tr>
<td>FVC (predicted %)</td>
<td>74.3 ± 9.0</td>
<td>72.7 ± 7.7</td>
<td>0.39</td>
</tr>
<tr>
<td>FEV₁ (predicted %)</td>
<td>73.2 ± 8.1</td>
<td>70.3 ± 6.1</td>
<td>0.07</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.77 ± 0.04</td>
<td>0.76 ± 0.06</td>
<td>0.22</td>
</tr>
<tr>
<td>TLC&lt;sub&gt;CT&lt;/sub&gt; (predicted %)</td>
<td>72.4 ± 12.5</td>
<td>79.2 ± 13.6</td>
<td>0.02</td>
</tr>
<tr>
<td>FVC/TLC&lt;sub&gt;CT&lt;/sub&gt; (%)</td>
<td>63.1 ± 12.7</td>
<td>57.1 ± 12.8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Except where indicated, numbers are means ± standard deviations.
PRISm = preserved ratio impaired spirometry, BMI = body mass index, FVC = forced vital capacity, FEV₁ = forced expiratory volume in 1 second, TLC<sub>CT</sub> = total lung capacity measured on CT, FVC/TLC<sub>CT</sub> = ratio of forced vital capacity to total lung capacity measured on CT, PSE = paraseptal emphysema, CLE = centrilobular emphysema
* Data are numbers of subjects, with percentages in parentheses.
Table 4. Multivariable linear regression models for FVC/TLC<sub>CT</sub> in smokers with PRISm

<table>
<thead>
<tr>
<th>Factors</th>
<th>Model: PSE</th>
<th></th>
<th></th>
<th></th>
<th>Model: CLE</th>
<th></th>
<th></th>
<th></th>
<th>Model: PSE+CLE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>p value</td>
<td>Estimate</td>
<td>95% CI</td>
<td>p value</td>
<td>Estimate</td>
<td>95% CI</td>
<td>p value</td>
<td>Estimate</td>
<td>95% CI</td>
</tr>
<tr>
<td>PSE, presence</td>
<td>-2.84</td>
<td>-8.24 to 2.58</td>
<td>0.30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-0.30</td>
<td>-6.07 to 5.46</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLE, presence</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-13.3 to -1.80</td>
<td>0.02</td>
<td>-11.7 to -0.55</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, per 1-year increase</td>
<td>-0.72</td>
<td>-1.01 to -0.42</td>
<td>&lt;0.01</td>
<td>-0.76</td>
<td>-1.11 to -0.38</td>
<td>&lt;0.01</td>
<td>-0.76</td>
<td>-1.05 to -0.47</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>-0.22</td>
<td>-8.35 to 7.91</td>
<td>0.96</td>
<td>0.73</td>
<td>-10.9 to 9.29</td>
<td>0.86</td>
<td>0.73</td>
<td>-7.26 to 8.71</td>
<td>0.86</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, per 1-kg/m$^2$ increase</td>
<td>-0.18</td>
<td>-0.90 to 0.54</td>
<td>0.63</td>
<td>-0.36</td>
<td>-0.11 to 0.85</td>
<td>0.32</td>
<td>-0.36</td>
<td>-1.09 to 0.36</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack-years, ≥ 20 pack-year</td>
<td>-0.78</td>
<td>-8.44 to 6.89</td>
<td>0.84</td>
<td>-0.92</td>
<td>-8.54 to 7.17</td>
<td>0.80</td>
<td>-0.83</td>
<td>-8.32 to 6.65</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status, current</td>
<td>-6.41</td>
<td>-12.6 to -0.26</td>
<td>0.04</td>
<td>-6.28</td>
<td>-16.9 to -3.13</td>
<td>0.04</td>
<td>-6.22</td>
<td>-12.2 to -0.22</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Each model was adjusted for age, sex, BMI, smoking pack-years, smoking status and facilities.
FVC/TLC<sub>CT</sub> = ratio of forced vital capacity to total lung capacity measured on CT, PRISm = preserved ratio impaired spirometry, PSE = paraseptal emphysema, CLE = centrilobular emphysema
Figures Legends

Figure 1. Study population flow chart

PRISm = preserved ratio impaired spirometry

Figure 2. Distribution of emphysema subtypes and lung functions in never-smokers and smokers with ≥ 10 pack-years undergoing CT lung screening.

The forced expiratory volume in 1 second (FEV₁, % predicted) is plotted on the x-axis, and the forced expiratory volume in 1 second to the forced vital capacity ratio (FEV₁/FVC) is plotted on the y-axis. The horizontal line represents the threshold for airflow limitation (FEV₁/FVC = 0.70), and the vertical line represents the threshold between mild and moderate airflow limitation (FEV₁ % predicted = 80%). The subjects with PSE or CLE are plotted as magenta (or orange) in each panel. PRISm = preserved ratio impaired spirometry, PSE = paraseptal emphysema, CLE = centrilobular emphysema

Figure 3. Prevalence of emphysema subtypes in PRISm according to smoking exposure

a) Emphysema subtypes distribution in PRISm, b) Prevalence of coexistence of PSE and CLE in smokers with PRISm

PSE = paraseptal emphysema, CLE = centrilobular emphysema, PRISm = preserved ratio impaired spirometry, ADE = advanced destructive emphysema

Figure 4. Representative image of smokers with PRISm absent or present emphysema.

Case (a) is 61 year-old male, and absent neither PSE nor CLE. Case (b) is 66 year-old male, and present both PSE (arrow) and CLE (circled). Both cases were comparable to lung functions (FVC %predicted; 74.7% and 79.6%, FEV₁ %predicted; 73.5% and 71.5%, and FEV₁/FVC; 0.80
and 0.75), but FVC/TLC_CT was lower in case (b) than case (a) (86.7% and 58.9%).
References


(PRISm) is associated with features of and progression to obstructive lung disease, Scientific Reports. 10 (2020). https://doi.org/10.1038/s41598-020-61932-0.


2116 subjects with age ≥ 40 years underwent chest CT for lung cancer screening and spirometry

298 excluded
  - Light-smoker
  - Abnormal CT findings
  - Lack of demographic data
  - Insufficient inspiratory chest CT
  - >90 days between CT and spirometry

Never-smoker
  - n = 1046
    - normal spirometry
      - n = 914
    - PRISm
      - n = 86
    - airflow limitation
      - n = 46

Smoker with ≥ 10 pack-year
  - n = 772
    - normal spirometry
      - n = 516
    - PRISm
      - n = 87
    - airflow limitation
      - n = 169
Supplemental Materials

The prevalence and physiological impacts of centrilobular and paraseptal emphysema on CT in smokers with Preserved Ratio Impaired Spirometry

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\textsuperscript{*}YS and TS contributed equally to this work.
Supplemental Methods

Study subjects

This study retrospectively evaluated data of spirometry and full inspiratory chest CT. Non-smokers and smokers aged 40 years or older who underwent chest CT for lung cancer screening and spirometry without bronchodilator were consecutively enrolled at four facilities and the eligibility for the present analyses was assessed. The exclusion criteria were 1) a history of lung resection, 2) chest CT abnormalities extending to more than one lobe (such as consolidations, atelectasis, tumors, pneumothorax and thoracic deformity), 3) missing information on smoking status or light-smokers (< 10 pack-years), 4) more than 90 days between spirometry and CT scanning, and 5) insufficient inspiratory chest CT defined as FVC>TLC\text{CT}. In the Tsukuba Medical Center, total 770 subjects underwent chest CT from November 2019 to September 2021. Nine subjects had abnormal CT findings or insufficient inspiratory CT, 155 subjects were missing demographic data, and 27 subjects were light-smoker. Ultimately, 579 subjects completed CT analyses. In the Kitano Hospital, total 356 subjects underwent chest CT for lung cancer screening from August 2012 to June 2014. Eleven subjects lacked demographic data, 13 subjects had abnormal CT findings or insufficient inspiratory CT, 4 subjects failed spirometry, and 30 were light-smokers. In the Takeda Hospital, total 885 subjects underwent chest CT from April 2016 to November 2020. Thirty subjects had abnormal CT findings or insufficient inspiratory chest CT, and 90 subjects were light-smokers. In the fourth facility (Terada Clinic, Respiratory Medicine and General Practice, Himeji), total 340 outpatients or subjects underwent chest CT for lung cancer screening from October 2018 to August 2020. Sixty-six subjects lacked demographic data, 41 subjects had abnormal CT findings or insufficient inspiratory CT, 42 subjects performed spirometry more than 90 days apart from chest CT scanning and 14 subjects were light-smokers.
Visual emphysema assessments

Six CT-experienced pulmonologists with at least 5-year experiences and a chest radiologist with 15-year experience performed visual emphysema analysis based on the Fleischner Society classification system [1]. CLE was classified as trace, mild, moderate, confluent or advanced destructive, while PSE was classified as mild or substantial [1]. The category of panlobular emphysema was not used in this study, as it is applied to patients with α1-antitrypsin deficiency [1]. Before assessing visual emphysema score in the study population, the analysts scored training CT datasets and substantial discordance was reviewed by the analysts to obtain consensus. Each CT scan was assessed by two analysts without knowledge of clinical information. When the assessment was disagreed among them, the final decisions was made by a chest radiologist. The images were viewed at window width 700 Hounsfield Unit and window level -750 Hounsfield Unit. The CT slice thickness was 0.5 to 1.25 mm. The weighted kappa coefficient was calculated for the severity of CLE and PSE. The severity of CLE (none/trace/mild/moderate/confluent/advanced destructive) was weighted from 0 to 5, and that of PSE (none/mild/substantial) was weighted from 0 to 2.

Reference
### Supplemental Table 1. Observer agreement for visual CT assessment

<table>
<thead>
<tr>
<th>Observer</th>
<th>No. of chest CT scans</th>
<th>PSE agreement</th>
<th>Weighted kappa coefficient for PSE</th>
<th>CLE agreement</th>
<th>Weighted kappa coefficient for CLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observer 1 vs Observer 2</td>
<td>578</td>
<td>97.8 %</td>
<td>0.94</td>
<td>99.0 %</td>
<td>0.99</td>
</tr>
<tr>
<td>Observer 3 vs Observer 4</td>
<td>874</td>
<td>90.2 %</td>
<td>0.73</td>
<td>90.5 %</td>
<td>0.83</td>
</tr>
<tr>
<td>Observer 3 vs Observer 5</td>
<td>246</td>
<td>85.0 %</td>
<td>0.81</td>
<td>76.8 %</td>
<td>0.83</td>
</tr>
<tr>
<td>Observer 3 vs Observer 6</td>
<td>120</td>
<td>85.8 %</td>
<td>0.81</td>
<td>70.0 %</td>
<td>0.90</td>
</tr>
</tbody>
</table>

PSE = paraseptal emphysema, CLE = centrilobular emphysema
Supplemental Table 2. Subject’s characteristics who underwent inspiratory and expiratory chest CT

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>67</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70.3 ± 11.4</td>
</tr>
<tr>
<td>No. of males*</td>
<td>56 (83.6%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1 ± 4.3</td>
</tr>
<tr>
<td>Smoking status, current*</td>
<td>30 (44.8%)</td>
</tr>
<tr>
<td>Pack-years, ≥ 20 pack-year*</td>
<td>59 (88.1%)</td>
</tr>
<tr>
<td>FVC (predicted %)</td>
<td>82.1 ± 20.9</td>
</tr>
<tr>
<td>FEV₁ (predicted %)</td>
<td>72.0 ± 27.2</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.67 ± 0.14</td>
</tr>
<tr>
<td>TLC&lt;sub&gt;CT&lt;/sub&gt; (predicted %)</td>
<td>88.3 ± 13.8</td>
</tr>
<tr>
<td>FVC/TLC&lt;sub&gt;CT&lt;/sub&gt; (%)</td>
<td>54.9 ± 15.7</td>
</tr>
</tbody>
</table>

Lung function categories
- Normal spirometry*            | 18 (26.9%) |
- PRISm*                        | 14 (20.9%) |
- Airflow limitation*           | 35 (52.2%) |

Except where indicated, numbers are means ± standard deviations.

BMI = body mass index, FVC = forced vital capacity, FEV₁ = forced expiratory volume in 1 second, TLC<sub>CT</sub> = total lung capacity measured on CT, FVC/TLC<sub>CT</sub> = ratio of forced vital capacity to total lung capacity measured on CT, PRISm = preserved ratio impaired spirometry

*Data are numbers of subjects, with percentages in parentheses.
**Supplemental Table 3. Correlation between FVC/TLC\textsubscript{CT} and inspiratory-expiratory CT air-trapping indexes**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Correlation coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expiratory low attenuation volume (%)</td>
<td>-0.55</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Expiratory mean lung density (HU)</td>
<td>0.56</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Expiratory and inspiratory mean lung density ratio</td>
<td>-0.51</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Correlation between FVC/TLC\textsubscript{CT} and other CT indexes were calculated with Pearson’s correlation test. FVC/TLC\textsubscript{CT} = ratio of forced vital capacity to total lung capacity measured on CT, HU = Hounsfield Unit.